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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/194,889	08/23/1999	LILI FENG	TSRI540.1	3717

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	19

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/194,889	Applicant(s) FENG et al.
	Examiner Christine Saoud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 16, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 6, 7, 18, 20-24, and 26-31* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 6, 7, 18, 20-24, and 26-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 19, 25 and 33 have been canceled and claims 1, 6, 7, 18, 20, 21, 26 and 27 have been amended as requested in the amendment of paper #16, filed 03 July 2002. Claims 1-3, 6-7, 18, 20-24, 26-31 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 03 July 2002 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

5. Claims 1-3, 6-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to "conferring resistance to endotoxic shock" by administering OB-R agonist ligand. However, endotoxic shock is an extremely acute condition, it is not predictable, and one of ordinary skill in the art would not accept that administration of OB-R agonist ligand would be capable of achieving the required result of conferring resistance to endotoxic shock within the necessary period of time. The specification provides no guidance nor working examples as to how such could be achieved. Furthermore, OB receptor is a molecule which will downregulate upon activation, therefore, it is not clear how prior administration in anticipation of endotoxic shock would result in a system that is responsive enough to OB-R agonist ligand to result in resistance to endotoxic shock. Accordingly, it is concluded that it would require undue experimentation to determine how to use the claimed invention.

6. Claims 18, 20-24 and 27 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record in paper #11.

Applicant argues at page 6 of the response that "compounds including cytokines are well known to one of ordinary skill in the art and that such a person would consider the invention reasonably to include any molecule that is known or could readily be evaluated with the methods of the invention" and that "determination of a compound having the requisite activity is not undue". This argument is not persuasive because enablement of the claimed invention requires that one of ordinary skill in the art be able to practice the claimed method without undue experimentation. As the claims encompass all agents which regulate expression of the Ob-R, the claims encompass such things as antisense, ribozymes, and other expression regulatory agents, which are not predictive one form the other. Regulation of gene expression is unpredictable, administration of antisense and gene therapy is unpredictable, the instant specification provides no guidance for such methods of using these kinds of agents, and it would require a substantial inventive contribution by the skilled artisan to practice the method as it is broadly claimed. Applicant argues that one could perform an assay to ascertain appropriate inducers for use, but this argument is akin to a "wish to know" for those agents which could be used in the claimed method and would require the skilled artisan not only to identify which agents may have potential in the claimed method, but also require the skilled artisan to develop the experimental protocol for the method to be function, which clearly demonstrates that the specification contains subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as it is currently claimed.

With regard to claim 26 (Applicant indicates claim 27, but it should be 26), Applicant argues that the claim as written is enabled. This argument is not persuasive. The instant specification fails to provide a single example of the treatment of a patient by administration of IL-6 and OB protein. Furthermore, as there are a multitude of conditions in which OB protein has been implicated, one of ordinary skill in the art at the time the instant invention would not reasonably expect the administration of the set amounts of IL-6 and OB protein recited in the instant claim to be effective for treatment of all such conditions. Different disease states and conditions which are associated with OB, and reduced OB receptor, are not regulated in the same manner, and therefore, would not be expected to be treated in the same manner. For example, as a condition characterized by OB resistance in which the defect is at the level of the receptor, the administration of OB or an agent which induces OB expression would be useless because no amount of OB is going to make up for the defective receptor. As the instant specification fails to provide a single example of treatment of a patient, the unpredictability of the art with regard to mechanisms of disease, the lack of guidance in the specification and the prior art regarding the claimed invention, it would require undue experimentation of one of ordinary skill in the art to practice the invention as claimed, absent evidence to the contrary.

Claim 27 is now directed to a method of inducing OB receptor expression in an animal by administration of IL-6 and OB protein. However, OB administration results in binding of the OB receptor and subsequent downregulation of the receptor. There is not a single example in the instant specification which coadministered IL-6 and OB and then determined that OB receptor

expression was induced. One of ordinary skill in the art would not expect this result and therefore, the claims are not enabled.

Claim Rejections - 35 USC § 102/103

7. Claims 18, 20-24, 26, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grunfeld et al. (J. Clin. Invest. 97(9): 2152-2157, 1996) for the reasons of record in paper #14.

Grunfeld et al. disclose that endotoxins and cytokines (related to inflammation and infection) induce expression of leptin/OB in response to infection. It is the expression of leptin/OB and the resultant secretion of leptin/OB which is determined to contribute to the anorexia of infection. Based on these findings, one of ordinary skill in the art at the time of the instant invention would readily ascertain that the OB is beneficial to the anorexic response and that the inflammatory endotoxins and cytokines enhance this response by inducing expression of endogenous OB, and therefore, the co-administration of the two compounds would be useful for treating conditions requiring anorexia, or weight loss. Therefore, treatment of a patient with obesity with an OB-receptor agonist, such as OB, and an agent which induces expression of OB, such as LPS, TNF, IL-1, IL-6, and INF, would have been *prima facie* obvious in light of the teachings of Grunfeld et al., absent evidence to the contrary. One would be motivated to use the combination of agents because the administration an agent which induces expression of OB would enhance the anorexic response and would increase the patient's own system to treat the obesity.

Applicant argues at page 7 of the response that treatment of LPS increases the expression of the OB receptor not OB. This statement is noted, but does not appear to influence the grounds of rejection. Applicant may have discovered another biological effect of LPS treatment, such as increased expression of OB receptor, but the art of Grunfeld et al. still discloses that endotoxins and cytokines increase expression of leptin/OB in response to infection.

Applicant further argues that the amount of weight loss exhibited in the instant specification is greater than reported in the literature, and therefore, provides unexpected advantages. This argument is not persuasive because a measured difference of 10% in the art compared to 16% in the instant application does not appear to be a significant or unexpectedly greater amount of weight loss. The methods are not identical and based on the errors involved in measuring, this amount of variation in the weight loss appears to be within normal experimental error and does not represent an unexpected result, absent evidence to the contrary.

Conclusion

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud